

937176

Food and Drug Administration Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Michael Friedman
Executive Vice President and Chief Operating Officer
Purdue Pharma L.P.
The Purdue Frederick Company
One Stamford Forum
201 Tresser Boulevard
Stamford, CT 06901-3431

JAN 17 2003

RE: NDA 20-553

OxyContin® (oxycodone HCl controlled-release) Tablets

MACMIS ID# 11400

WARNING LETTER

Dear Mr. Friedman:

This Warning Letter (revised) concerns the dissemination of promotional materials for the marketing of OxyContin® (oxycodone HCl controlled-release) Tablets by Purdue Pharma L.P. ("Purdue"). Specifically, we refer to two journal advertisements for OxyContin that recently appeared in the *Journal of the American Medical Association* (JAMA), one in the October 2, 2002 issue (A7038) (the "October Ad") and one in the November 13, 2002 issue (A7087) (the "November Ad"). The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these advertisements and has concluded that they are in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C.§§ 331(a) and (b), 352 (n), and its implementing regulations.

Your journal advertisements omit and minimize the serious safety risks associated with OxyContin, and promote it for uses beyond which have been proven safe and effective. Specifically, your journal advertisements fail to present in the body of the advertisements <u>any</u> information from the boxed warning in the approved product labeling (PI) for OxyContin regarding the potentially fatal risks associated with the use of OxyContin and the abuse liability of OxyContin, which is a Schedule II controlled substance, and make unsubstantiated efficacy claims promoting the use of OxyContin for pain relief. Your journal advertisements also understate the minimal safety information that is presented.

Your advertisements thus grossly overstate the safety profile of OxyContin by not referring in the body of the advertisements to serious, potentially fatal risks associated with OxyContin, thereby potentially leading to prescribing of the product based on inadequate consideration of risk. In addition, your journal advertisements fail to present in the body of the advertisements

critical information regarding limitations on the indicated use of OxyContin, thereby promoting OxyContin for a much broader range of patients with pain than are appropriate for the drug. The combination in these advertisements of suggesting such a broad use of this drug to treat pain without disclosing the potential for abuse with the drug and the serious, potentially fatal risks associated with its use, is especially egregious and alarming in its potential impact on the public health.

Background

OxyContin was approved on December 12, 1995. Because the drug has a potential for abuse and has risks associated with its use that are serious and potentially fatal, the current PI for OxyContin contains a boxed warning that includes the following important information (emphasis in original):

- OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.
- Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
- OxyContin 80mg and 160mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.
- OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Because of safety concerns, there are important limitations on the indicated use of OxyContin. The boxed warning contains the following bolded statements:

- OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.
- OxyContin Tablets are NOT intended for use as a prn analgesic.

The Precautions section of the OxyContin PI contains further bolded limitations on the appropriate use of OxyContin, namely:

• OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).

- OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.
- OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.
- OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

Moreover, because of the serious risks associated with OxyContin, it is contraindicated in a number of patient populations, including:

- Patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment)
- Patients with acute or severe bronchial asthma or hypercarbia
- Any patient who has or is suspected of having paralytic ileus.

Lack of Important Risk Information

Promotional materials are misleading if they fail to reveal material facts relating to potential consequences that may result from the use of the drug as recommended or suggested by the materials. Promotional materials are also misleading if they fail to include a balanced presentation of information relating to contraindications, warnings, precautions, and side effects associated with the use of a drug along with the presentation of promotional claims relating to the effectiveness and safety of the drug. Your journal advertisements are misleading because they make prominent claims of effectiveness for pain relief, but omit from the body of the advertisements crucial facts related to the serious, potentially fatal safety risks associated with the use of OxyContin, the potential for OxyContin to be abused, and the limitations on its appropriate indicated use.

Omission of material facts related to abuse liability and fatal risks

Specifically, your November Ad contains a two-page spread picturing a man fishing with a boy and featuring the prominent headline "THERE CAN BE LIFE WITH RELIEF." The words "LIFE WITH RELIEF" are the largest in the advertisement. The ad also features a graphic of two paper medication dosage cups with "8 AM" and "8 PM" next to them. The logo for OxyContin is right below, with the prominent tagline "IT WORKS." Your October Ad promotes "WHEN IT'S TIME TO CONSIDER Q4-6H OPIOIDS...REMEMBER, EFFECTIVE RELIEF TAKES JUST TWO." The claim "REMEMBER, EFFECTIVE RELIEF TAKES JUST TWO" is prominently highlighted in the middle of the ad, surrounded by comparative graphics of dosage cups which show only two dosage cups for OxyContin, as compared to six dosage cups for the other drugs. As with the November Ad, the logo for

OxyContin is directly under the graphic of the two dosage cups, with the prominent tagline "IT WORKS." Therefore, the principal message of both advertisements appears to be that OxyContin offers effective pain relief and has convenient dosing.

These ad presentations, however, fail to present in the body of the advertisements critical safety information related to the use of OxyContin needed to balance these broad claims promoting its efficacy for pain relief. Neither one of your ads presents in the body of the advertisements any information from the boxed warning discussing OxyContin's potential for abuse and the related considerations when prescribing the drug. Neither one of your ads presents in the body of the advertisements any information from the boxed warning disclosing that the drug can be fatal if taken by certain patients or under certain conditions. It is particularly disturbing that your November Ad would tout "Life With Relief," yet fail to warn that patients can die from taking OxyContin.

These ad presentations are accompanied by a brief summary of the prescribing information for OxyContin, including the boxed warning, and the ads include a reference to the brief summary. However, presenting important risk information in this manner is not in accordance with FDA's prescription drug advertising regulations. See 21 CFR 202.1(e)(3)(i) (Untrue or misleading information in any part of the advertisement will not be corrected by the inclusion in another distinct part of the advertisement of a brief statement containing true information relating to side effects, contraindications, and effectiveness of the drug.) The typical physician reviewing an advertisement for a prescription drug would expect the most serious risks associated with the drug to be included in the body of the ad. The body of these ads contains no discussion of the potentially fatal risks associated with the drug and its potential for abuse. Moreover, the expectation that the most relevant risks have been disclosed in the body, rather than the brief summary, of your ads is exacerbated by having a statement in the body of your ads that begins "The most serious risk..." implying that what follows is a complete statement of the drug's most serious risks, not that there are other, more serious risks to be aware of. Therefore, the language in the body of your ads reinforces the impression that the most serious risks have been disclosed, when in fact they have not.

Minimization of risk in information presented

Your ads not only omit these important risks, but also understate the minimal safety information that you do disclose in the body of the advertisements, thus completely misrepresenting the safety profile of the drug. Your ads state that "The most serious risk with opioids, including OxyContin®, is respiratory depression." This statement suggests that there are no specific safety considerations for OxyContin related to respiratory depression, which is false or misleading and could lead to prescribing of the product based on inadequate consideration of risk. This statement also fails to warn that this risk can be a fatal one. As stated in the boxed warning, OxyContin has two tablet strengths that are for use in opioid-tolerant patients only, because they can cause fatal respiratory depression when administered to patients not previously exposed to opioids. Also, the boxed warning states that OxyContin tablets are to be swallowed whole and not broken, crushed or chewed, because that leads to rapid release and absorption of a potentially fatal dose of OxyContin. It is especially troubling that your ads tout the dosing convenience of

OxyContin as a benefit, but fail to warn of these associated serious safety risks that come from its controlled-release formulation.

Your advertisements, in this context, also minimize the most common adverse events associated with OxyContin by describing "Common opioid side effects" rather than side effects and safety risks that have been seen with OxyContin itself. In addition, your advertisements state that "OxyContin is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated," without giving the specific contraindications noted above. By essentially suggesting that no safety or tolerability issues have been seen specifically with OxyContin, and by implying that OxyContin therapy is not associated with the serious and significant risks outlined above, your advertisements grossly misrepresent the safety profile of OxyContin. This implication is false or misleading and raises significant public health and safety concerns.

Overbroadening of Indication

Your advertisements suggest that OxyContin can be used in a much broader range of pain patients than has been proven to be safe and effective. This is even more problematic from a public health perspective given the serious safety risks associated with the drug and the serious deficiencies in the safety information presented in your advertisements.

The only indication information presented in the body of the advertisements (indeed, the only information from the boxed warning included at all as part of the body of these advertisements) is the partial language from the Indications and Usage section of the PI, "For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time," which you present by itself at the top of these advertisements. In the November Ad, this information is located in the upper left-hand corner of the picture on the first page of the spread, in small white type over a background of green leaves and blue sky. It is also the only writing on that page. This information is not prominent, and is not adequately communicated, especially in contrast to the prominent claim of "THERE CAN BE LIFE WITH RELIEF" and all the other text of the advertisement on the next page. Similarly, in the October Ad, this partial indication language is included at the top of the ad in a much smaller typesize than the prominent claims related to "effective relief" with the drug. These presentations are insufficient to give appropriate context and balance to your claims broadly promoting the use of this drug for pain relief. In addition, in your November Ad, you portray a seemingly healthy, unimpaired man out fishing and taking care of a child, rather than depicting a more typical person with persistent, moderate to severe pain taking OxyContin. Therefore your advertisements fail to adequately communicate the actual indication for OxyContin and suggest its use for pain relief in a much broader range of patients than indicated.

In addition, your advertisements fail to present in the body of the advertisements the other important limitations on the indicated use of OxyContin as noted above. Although you prominently claim effective "relief" and that the product "works," you fail to qualify that, as per the boxed warning, OxyContin is not intended to be used as a prn (as needed) analgesic. In fact, your October Ad prominently directs physicians to prescribe OxyContin "WHEN IT'S TIME TO

CONSIDER Q4-6H OPIOIDS," which could easily suggest prn use. (Q4-6H indicates 4-6 hours of effectiveness.)

Also of concern, your advertisements, and in particular, your October Ad, represent the dosing convenience of OxyContin by showing dosage cups of the type used to dispense medication in a hospital setting, along with your broad claims of efficacy. The body of the advertisements, however, fails to present the important limitations on the use of OxyContin restricting it to certain hospitalized patients, as described in the OxyContin PI. Most notably, the PI states that OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established. OxyContin is also not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time. The PI also states that OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain). You fail to present in the body of your advertisements any of these important limitations, thus suggesting the use of OxyContin in inappropriate patients.

Conclusions and Requested Actions

You have disseminated promotional journal advertisements that fail to disclose in the body of the advertisements serious and significant risks associated with the use of OxyContin and important limitations on the indicated use of the drug.

Because of the significant public health and safety concerns raised by your advertisements, we request that you provide a detailed response to the issues raised in this Warning Letter. This response should contain an action plan that includes:

- 1) Immediately ceasing the dissemination of these advertisements and all other promotional materials that contain the same or similar violations outlined in this letter.
- 2) Providing a plan of action to disseminate accurate and complete information to the audience(s) that received the misleading messages.
- 3) A written statement of your intent to comply with "1" and "2" above.

Please respond in writing to DDMAC by January 24, 2003 of your intent to comply with DDMAC's request. If you have any questions or comments, please contact Mark Askine or Carol Barstow by facsimile at 301-594-6759 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for OxyContin, and may determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #11400 in addition to the ANDA number.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was sign	gned electronically and
this page is the manifestation of the electronic signature.	

/s/

Thomas Abrams 1/17/03 04:31:31 PM

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

WHEN IT'S TIME TO CONSIDER Q4-6H OPIOIDS...



REMEMBER, EFFECTIVE RELIEF TAKES JUST TWO

The most serious risk with opioids, including OxyContin®, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating and weakness.

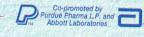
OxyContin[®] is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. (See **Contraindications** section in package insert.)



O12h
OXYCONTIN® (I)
(OXYCODONE HCI CONTROLLED-RELEASE) TABLETS
IT WORKS

Please read brief summary of full prescribing information, including boxed warning, on reverse side.





OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illic it. This should be considered when prescribing or dispension of the considered when prescribing or dispension or Oxycocone can de abuseo in a manner similar to omer opioid agonists, legal or illic-it. This should be considered when prescribing or dispensing OxyCorbin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydroct ride indicated for the management of moderate to severe pain when a continuo around-the-clock analgesic is needed for an extended period of time.

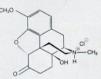
OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause latal respiratory depression when administered to patients not previously exposed to opioids.

OxyContile Tablets are to be swallowed whole and are not to be bro-ken, Chewed, or crushed. Taking broken, Chewed, or crushed oxyContile Tablets leads to rapid release and absorption of a potentially fatal Dose of OxyCo

DESCRIPTION

OxyContin* (oxycodone hydrochloride controlled-release) Tablets are an opicid analgesic supplied in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for oral administration.



INDICATIONS AND USAGE

OxyContin* Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analysis is needed for an extended period of time.

OxyContin is NOT intended for use as a pm analgesic.

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Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analysisis, such as non-steroidal arin-inflammatory drugs and additionable to the control of the principage of the control of the principage of the

Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society, Ony-Control is not indicated for pain in the immediate postoperative period (the first 12-24 hours following supery), of if the pain is mild, or not expected to persist for an extended period of time. Oxy-Control is orly indicated for postoperative use if the patient's already receiving the drug prior to surgery or if the post overative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See America pins Society nucleilloss.)

CONTRAINDICATIONS

NON-critin's contraindicated in patients with known hypersensitivity to coycodore, or in any situation where opinids are contraindicated. This includes patients with significant respiratory depression (in unmornitated settings of the absence of resuscitative capitament), and patients with audio reserve bronchial safety hypercarbia. One Cordin is contraindicated in any patient, who has or is suspected of having paralytic less. WARNINGS

WARNINGS

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR

CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED DXYCONTIN TABLETS LEADS TO RAPID RELEASE

AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OxyCoefin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tal strengths may cause fatal respiratory depression when administered to patients not previous

exposed to opioids.

OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxyCondone equivalent dosages of 160 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients about be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse Abuse and Diversion of Opioids

Misuse, Abuse and Diversion of Opinids
Oxycocone is an opinid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.
Oxycocone can be abused in a manner similar to other opinid agonists, legal or illicit. This should be considered when prescripting or dispersing to QoCornin in shallmost where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
OxyCornin has been opported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opinid and pose a significant risk to the abuser that could result in result in the uncontrolled delivery of the opinid and pose a significant risk to the abuser that could result in result in the uncontrolled delivery of the opinid and pose as significant risk to the abuser that could result in result in the uncontrolled delivery of the opinid and pose as significant risk to the abuser that could result in result in the proper management of pain. The abuser that could risk risk in the discould result in the proper management of pain. The relations professionals should contain the State Professional Learning Beard or State Certifical Substances Authority for information on how to prevent and detect abuse or diversion of this product. Interactions with Alcohol and Drugs of Abuse
Oxycocone may be expected to be have additive effects when used in conjunction with alcohol, other opinids, or illicit drugs that cause certimal nervous system depression.

DRUG ABUSE AND ADDICTION

OnyConfirm' is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II con-trolled substance. Onycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

learn or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

Thug-seeding behavior is very common in addicts and drug abusers. Drug-seeding lactics include in the properties of the properties of office hours, reflectable to undergo appropriate examination, testing or referral, expeated lists of prescriptions, tempering with prescriptions and relutance to provide provide medical records or contact information for other between psysicianity. Dioctor shopping to obtain addistance or provide provide provides and provides a

Respiratory Depression

respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin*, as with all opi-dio agonists. Respiratory depression is a particular problem in elderly or debitated patients, usually following large initial loses in non-tolerant patients, or when opioids are given in conjunction with other agents that depressi-

respiration.

Oxygodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or our pulmonals, and in patients having a substantially diseased respiratory reserve, hypoxic, hypercapinic, or pre-existing respiratory depression, in such patients, even usual threspace disease of oxygodone may deemade respiratory divine to the point of agrees, at these patients alternative non-policy expects should be considered, and opioids should be employed only under careful mendical supervision at the lowest effective disea.

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of previous processors, and may be markedly exaggerated in the presence of head injury, intracra-nial lesions, or other sources of pre-existing increased intracrarial pressure. Oxycodome produces effects on pupility response and consciouses which may obscure neurologic signs of suffer increases in intracra-rial pressure in patients with head injuries.

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood

pressure has been compromised by a depicted blood volume, or after concurrent administration with drugs such as phenotheranes or other agents which compromise vesorandor time. Depositione may produce or hossitio hypotension in ambutatory patients. Depositione, like all opicid analysisses of the morphine-type, should be administrated with caudion to patients in circulating shock, since vascotlation produced by the drug may further reduce cardiac output and blood pressure.

General

General

Opioid analogsiscs have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analogsisa outweigh the known risks of respiratory depression, attended mental state, and postural hypotheristin. Use of Oxycontin is associated with increased potential diseases and should be used only with custom in the following conditions: acute abcoholism; advenocracia insufficiency (e.g., Addison's disease), ONS depression or come; definite therems; delething patients; hypotheristics soorceited with respiratory depression, monarry or realt intention, and foote projections.

The administration of devocotion may operate convisions in patients, overee inpartment of legislate; put indicated and opinions of the patients of the pati

in combination with the usual doses of DxyCortin.
Interactions with Mitzed Against/Antagonist Optioid Analgesics
Approxistratoposis analgesics (e., partiagonie, publishine, and butorphanol) should be administered
caution to a patient who has received or is receiving a course of therapy with a pure opinid agonist
getis such as oxygodone. In this situation, mixed agonistization printagonist analgesics may reduce the anal
effect of oxygodone andoor may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Postoperative Use
OxyCodin is not indicated for pre-emptive analogesia (administration pre-operatively for the ma
of postoperative pain). on pursupportance passin.

DxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not have getal-field.

OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to per-sist for an extended period of time.

sist for an extended period of time.

OnyContin- is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderals to severe and persist for an extended period of time. Physicians should individualist treatment, moving from parenterial for an extended period of time. Physicians should individualist treatment, moving from parenterial to oral analysiscs as appropriate (See American Phall Society) guidelines to part of ongoing analysis therapy may be assisty continuous on the drug if appropriate lossing adjustments are made considering the procedure, other ones given the drug if appropriate lossing adjustments are made considering the procedure, other ones given the drug if appropriate lossing adjustments are made considering the procedure, other ones given the drug if appropriate lossing adjustments are made considering the procedure, other ones given the procedure of the procedur

DVSCART AND Automited Instituty.

DvyConfill and other morphine-like opioids have been shown to decrease bowel motify, lieus is a common postoperative complication, especially after intra-abdominal surgery with opioid analogesia. Caution should be taken to mortify for decreased bowel motify in postoperative patients receiving opioids Standard supportive therapy should be implemented.

Standard supportive trierapy singuild be in pointerined.

Use in Pancreatic/Billiary Tract Disease
Opcodone may cause spasm of the sphincher of Oddi and should be used with caution in patients with billiary tract disease, including acute pancreatris. Opioids like paycodone may cause increases in the serum

Fournable The register of the properties of the

The opicid abstractor or withdrawal syndrome is characterized by some or all of the following: restleness, lacimation, thisomhea, yearving, pesspiration, chills, myaliga, and mydisals. Other symptoms as may develop, locking, intribulity, anatory, braineste, portion, wakeness, abordinal carrants, insommasse, another's, womting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

- in general: opicids should not be abruptly discontinued.

 Information for Patients Carepivers

 If clinically advisable, patients receiving DayContin Tablets or their carepivers should be given the following information by the physician; nurse, pharmacist, or carepiver:

 1. Patients should be aware that DayContin Tablets contain oxycodorie, which is a morphine-like substance.

 2. Patients should be advised that DayContin Tablets vere designed to work properly only if swallowed whole DayContin Tablets will release all their contents at once if broken, chewied, or crushed, resulting in a risk of tatal overdose.
- or state oversouse.

 3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy, individualization of dosage is essential to make optimal use of this medication.

 4. Patients should be advised not to adjust the dose of DxyContin* without consulting the prescribing pro-

- fessional.

 Patients should be advised that OxyContin may impair mental and/or physical ability required for the per-formance of potentially hazardous tasks (e.g., dwinn); operating heavy machinery).

 Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects any occur. resembling in sentions implicy or death.
- Winners of childbearing potential who become, or are planning to become, pregnant should be advised to consult their planning the effects of analysiss and other drug use during pregnancy on themselves and their unborn child.

- selves and their unborn critic.

 Patients should be advised that OpCordin is a potential drug of abuse. They should protect it from their, and it should never be given to airyone other than the individual for whom it was prescribed, and it should never be given to airyone other than the individual for whom it was prescribed.

 Patients should be advised that they may pass among market years; facilities, but collectiony on in the should not their this is of no control.

 Patients should be advised that if they have been exherted relative to the patient of the self-should be advised that if they have been exherted to tage the OpCordin doze, patient weeks and observable that if they have been exherted to tage the OpCordin doze, patient provide a doze schedule to accompish a gradual discontinuation of the medication.

 Patients bundle be instituted to level pocyclorin as a source pace and of the reach of children when they control is no longer needed, the unused tablets should be destroyed by flushing down the tollet.

Occordin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with only or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analysis.

Drug-Drug Interactions

urup-trug interactions

Opcide analysiss, including OpyContin*, may enhance the neuronuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Osycodore is metabolized in part to opymophore six opcortonere P450 205. While this pathway may
be blocked by the skelety of drugs (e.g., certain cardiovascular drugs including amiodarone and quiridine
such that the part of t

We this AS Depressants

OxyContin', like all opioid analysess, should be started at 1/s to 1/s of the usual dosage in patients who are concurrently receiving other central nervous system depressants including setables or hypodics, peneral anesthedios, phenothisations, centrally acting and-emetics, transputices, and all other central nervous systems of the concurrently received and the concurrently received and the concurrent of the concurre

patients taking this class of drugs is appropriate.

Carcinogenesis, Mudagenesis, Impaliment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mudagenic in the following assays: Armes Salmonella and E. coll test with and without metabolic activation at doses of up to 5000 µg, chromosomal abertation test in human lymphocytes
in the absence of metabolic activation at doses of up to 1500 µg/mL and with abertation 46 hours after
exposure at doses of up to 5000 µg/mL, and in the in who bore marrow microprosues test in missismal levels of up to 45 µg/mL). Oxycodone was catalogenic in the human symptocyle chromosomal
assay in the presence of metabolic activation in the human chromosomal abertation set (all operation
equals to 150 µg/mL) at 24 µg/mL or 46 hours of exposure and in the mouse lymphona assay at doses
of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activafor.

Pregnancy

Pregnancy Technology 8: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg. respectively. These doses are 3 and 46 times a distribution dose of 160 mg/kg bases. The results did not review devine of harm for the distribution of the mg/kg bases. The results did not review devine or harm for the distribution of the mg/kg bases. The results did not not oppose the mg/kg bases have expected and well-controlled studies in pregnant women. Because arimal proproduction studies are not adward productive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Op/Cordin's not recommended for use in women during and immediately prior to labor and delivery because ona opioids may cause respiratory degression in the newtorn. Neonates whose mothers have been tak-ing opcodone chronically may exhibit respiratory depression and/or with/drawal symptoms, either at birth and/or in the nursery. **Nursing Mothers** Low concentrations of coycodone have been detected in breast mik. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is neceiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.

Geriatric Use
In controlled pharmacolinetic studies in elderly subjects (greater than 65 years) the clearance of approximate papered to be slightly reduced. Compared to young adults, the plasma concentrations of corpocions were presented of proximately 15%. Of the total number of subjects (445) in 15% of 15%

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of liberance, plasma dispositione measurements are usually not height in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or comprise cases.

Hepatic Impairment

A study of DxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/s to 1/s the usual doses and careful dose thration is warranted.

In patients with meral impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the con-centrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal result function. Does initiation should follow a conservative approach. Obsages should be adjusted according to the clinical statistics.

unner unterences
In pharmacoknetic studies, opiois-trakve females demonstrate up to 25% higher average plasma concentrations and greate frequency of typical opioid adverse events than makes, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at intrivioustratio dosages, and there was no makefemale difference detected for efficacy or adverse events in critical training.

AVERSE REACTIONS

The safety of DoyContim was evaluated in double-blind clinical trials involving 713 patients with modeation of the prior various enloques. In open-label studies of cancer pain, 187 patients received
to come and the various enloques. In open-label studies of cancer pain, 187 patients received
approximately 196 may per day.

Services adverse reactions which may be associated with OvyContin Tablet therapy in clinical use are those
solvened with other opioid analysesis, including respiratory depression, appear, respiratory arrest, and do
an even lesser degree) circulatory depression, hypothersion, or shock (see OVERDOSARE).

The onn-enforce adverse events seen on initiation of therapy with OvyContin are typical opioid side
effects. These events are obse-dependent, and their frequency deponds upon the dose, the clinical set
ring, the patient size of opioid denalpesia. The most frequent (>-5%) include: constipation, nauser
commonence, dizenses, synnifting, rurable, headacher, or younds, vestelling, and asterials,
in many cases the frequency of these events during initiation of the rapy may be minimized by the opioid and services of the opioid. Many of these adverse events will case or decrease in initiating in the place of the opioid and services of the opioid. Only of these adverse events will case or decrease in initiating in the place or opioid and service of the opioid. Only of these adverse events will case or decrease in initiating and service opioid event of the opioid and service opioid and mentales enlose or opioidene. The most common adverse events (>-5%) reported by patients at least once during therapy were.

	OxyContin (n=227) (%)	Immediate- Release (n=225) (%)	Placebo (n=45) (%)
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	-
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in DxyContin* treated patients with an incidence between 1% and 5%, in descending order of frequency they were ancreas, encourages, insormal, fever, confusion, durrhea, abdominal pain, dyspepsia, rash, a martie, explorite, dyspena, postural hypotension, chills, twitching, pastites, abunding ferams, florought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarkering experience.

General: accidental injury, chest pain, facial elema, malaise, neck pain, pain

veneral, autoreman injury, criest paint, indica externat, meable, reux paint, paint Cardiovascular, migraine, synchope, vasodiation, ST depression Oligestive: Osphagia, eructation, fatulence, gastrointestinal disorder, increased appetite, nausea and vorning, stornatios, iteus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropri-ate antidiuretic hormone secretion, thirst

Nervous zhoromal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucina-hon, hyperkinesia, hypesthesia, hypotonia, mulaise, paresthesia, setzures, speech disorder, stupor, tinni-tus, tremor, vertigo, withdrawal syndrome with or without setzures

Respiratory: cough increased, pharyngitis, voice alteration Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

ed libido, dysuria, hematuria, impotence, polyuria, urinary retention, uri-Urogenital: ameno

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progress-ing to stupor or coma, skaletal muscle flaccidity, cold and clarminy skin, constricted pupils, bradycardia, hypotension, and death.

repositions, an useful.

Deaths due to overdose have been reported with abuse and misuse of OxyContin*, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is fur-or injecting the or Case of the Case of the

In the treatment of coycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventiation. Supportive measures (including open gen and visopressors) should be employed in the management of circulatory shock and pulmonary edema concregativity operations as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defib-actions are considered to the control of the cardiac arrest or arrhythmias may require cardiac massage or defib-

Intestin.

The same pooled antagonists such as naloscore or nalmetere are specific antidotes against respiratory opprament from point overdose. Dipidid antagonists should not be admisstered in the absence of clinically signiment respiratory or cruniatory depression secondary to exprosione eventoes, in patients who are physicially dependent on any opioid against including QN/content*, an about or complete reversal of opioid effects
and prespirator and acute abstinance syndrome. The severity of the withdrawing syndrome produced with
depend on the degree of physical dependence and the dose of the antagonist administered. Please see
the prescribing information for the specific opioid antagonist for details of their proper use.

Managing Expected Opioid Adverse Experiences

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, specially those who are opioid-naive, will experience side effects. Frequently this side effects are not oxycontain are traveled, but may require evaluation and management. All requirements are selected to the effects are inclinated and related angerisselve and protypicatically will suit an experience of the effects of the effects of the effects of the effects of coldisis.

opionas. Other opioid-related side effects such as sedation and nausea are usually self-imited and often do not per-sist beyond the first few days. If inausea persists and is unacceptable to the patient, the timent with arithmet-ics or other modalises many relieve these symptoms and should be considered. Patients receiving (Dx/Cortión* may pass an intact maths* cytes" in the stort or via colostomy. These ghosts contain title or no residual approaches and are of no inclinad consequence.

SAFFTY AND HANDLING

SAFETY AND HANDLING

Opcontral Tables a solid dossage forms that contain oxycodone which is a controlled substance. Use morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

Objection has been targeted for their and diversion by criminals. Heathcare professionals should contact their State Professional Livensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

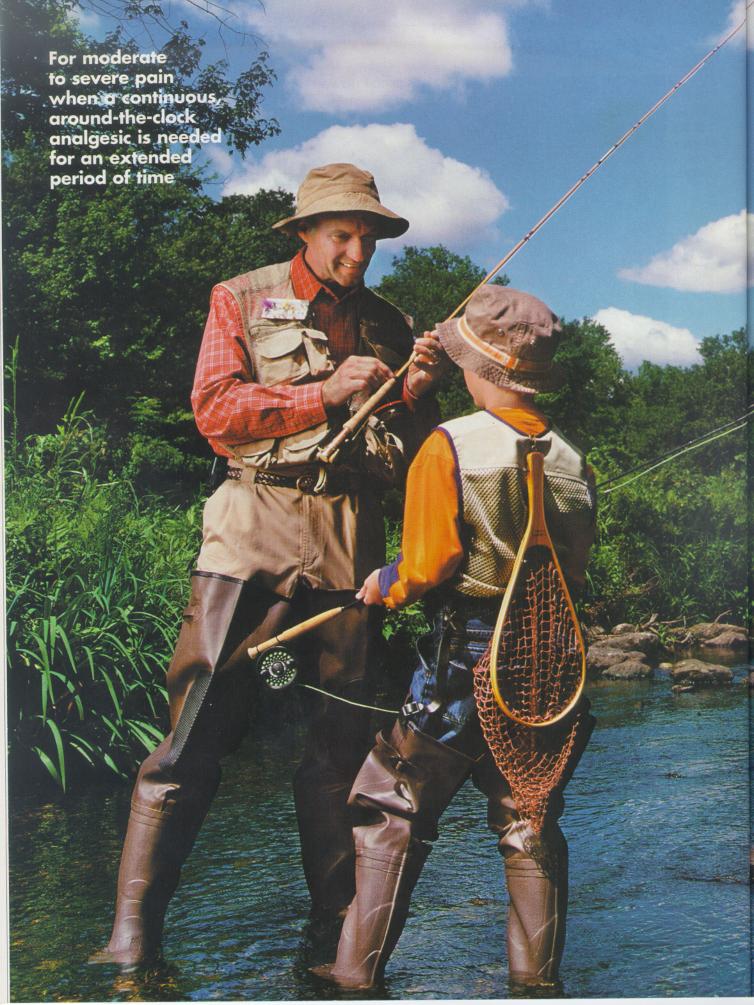
Store at 25°C (77°F); excursions permitted bothween 15°-30°C (58°-36°F).

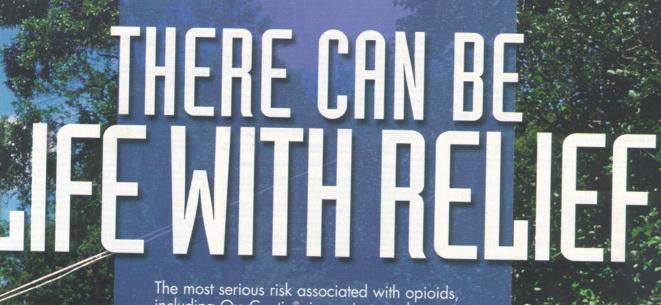
Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

DEA Order Form Required.

Purdue Pharma L.P., Stamford, CT 06901-3431 ©2001 Purdue Pharma L.P.

U.S. Patent Numbers 4,861,598; 4,970,075; 5,266,331; 5,508,042; 5,549,912; and 5,656,295





including OxyContin®, is respiratory depression. Common opioid side effects are constipation, nausea, sedation, dizziness, vomiting, pruritus, headache, dry mouth, sweating and weakness.

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated.

Please see Contraindications section in package insert.

Purdue is firmly committed to maintaining the highest standards of marketing practices in the industry while continuing to advance the proper treatment of pain in America. If Purdue's marketing and sales practices fail to meet this standard, we urge you to contact us at 1-888-690-9211.

OXYCODONE HCI CONTROLLED-RELEASE) TABLETS IT WORKS

Please read brief summary of prescribing information including boxed warning on reverse side.

Copyright 2002 Purdue Pharma L.P., Stamford, CT 06901-3431 A7087-FS PUR-4000927B.

*80 mg and 160 mg for use in opioid-tolerant patients only

WARNING

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illic. it. This should be considered when prescribing or dispensing DxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochlo-ride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin Tablets are NOT intended for use as a prn analgesic

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS INLY. These tablet strengths may cause fatal respiratory depried to patients not previously exposed to opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BRO-KEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE

OxyContin* (oxycodone hydrochloride controlled-release) Tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for oral administration.

INDICATIONS AND USAGE

OxyContin[®] Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin is NOT intended for use as a pm analgesic

Opcortion is NOT reterede for use as a prin integrence. The properties will be appropriate point along in Physicians should individualize treatment in every case, initiating therapy at the appropriate point along in progression from non-opioid analgetics, such as non-steroidal anti-inflammation's urbugs and exists minophen to policia in a plain or plant management such as outfield by the World Health Organization, the Agency for Healthcare Research and Quality (termety known as the Agency for Health Care Policy and Research), the Policiand on State Medical Shoats Model Guidetine, of the American Plant Society.

research, the Profession on Sales Membra Sales Social Souther Sales, or the America Sales Social Soc

Ox/Cortin' is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmontrated setting or the absence of resuscitative equipment), and patients with acute or severe bronchial addition typercarbia. Oxy Cortin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

INJUSTATION AND ATTEMPT OF STRAILDING WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED, TWING BROKEN, CHEWED OR CRUSHED DXYCONTHIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FAILA DOSE OF GOVERNOONE.

OXYCOMIN DO mg and 160 mg Tablets ARE FOR USE IN OPPOIDT-TOLERANT PATIENTS ONLY. These tablet strengths may cause latal respiratory depression when administered to patients not previously expected to plother.

exposes to opinids.

Ony Contin 80 mg and 160 mg Tablets are for use only in opicid-tolerant patients requiring daily oxycodence equivalent dosages of 160 mg or more for the 80 mg tablet and 220 mg or more for the 160
codence equivalent dosages of 160 mg or more for the 160 mg tablet and 220 mg or more for the 160
tolerant opinion of the 160 mg tablet and 160 mg tablet and 160 mg tablet opinion opinio

Oxycodone is an opioid aportst of the morphine-type. Such drugs are sought by drug abusers and peo-ple with addiction disorders and are subject to criminal diversion.

pie with addiction disorders and are subject to criminal diversion.

Osycolone can be abused in a manner smillar to other opioid agenists, legal or illicit. This should be considered when prescribing or depreving OxyCortin in shatators where the physician or pharmacist is concerned about an increased risk of missue, abuse, or diversion.

OxyCortin has been reported as being abused by crusting, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk the abuser that could result in vertices and death (see WarAMINGS and OTRUE ABUSE AND ADDICTION).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analysiscis in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in coming pain patients. to be rare. However, data are not avairable to establish the true incidence or addiction in chronic pain patients. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opi-nids, or flicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

OxyConlin' is a mu-agenist opioid with an abuse liability similar to morphine and is a Schedule II con-trolled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by computeive use, use for non-medical purposes, and continued use despit harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relaps

is common.

Drug-seeking behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated basis of prescriptions, tempering with prescriptions and relutacion to produce produce prescriptions or contact information for other theraping physicians (s). Dottor shapping addictions repeated and contact on a separate and distinct from physician dependence and tolerance. Physicians shapping addiction may not be accompanied by concurrent tolerance and operations of the physician dependence and tolerance. Physicians shapping and the physician shapping and the physician shapping and the physician shapping and the physicians that distinct is a decided by misuse for non-metical purposes, determine and operations of the physicians shapping and the physicians are physicians and the physicians are proposed by misuse for non-metical purposes, determine and operations of the physicians of physicians and the physicians are physicians and the physicians are physicians and the physicians and the physicians are physicians

pening and storage are appropriate measures that help to limit abuse of opicid drugs.

OnyContin consists of a dual-polymer matrix, intended for ror situs only, Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenterial abuse, the tablet excipients, especially late, can be expected for in local tissue necessits, infection, patients and mortal symmetric and increased risk of endocarditis and valuate heart injury. Parenterial drug abuse is commonly associated with transmission of infectious discesses such as hepatitis and HVI.

Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin*, as with all opi-oid apoids. Respiratory depression is a particular problem in elderly or debittated patients, usually following large intel doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress

respiration.

Opportions bround be used with externer caution in patients with significant chronic obstructive pulmon disease or on pulmonals, and in patients having a substantially decreased respiratory reserve, hypoprocuratio, or pre-busting respiratory depression. In such staffsets, even usual improvation of concluding a superior of control many decrease respiratory drive to the point of apnea, in these patients alternative non-opioid are passes, should be considered, and opioids should be employed only under careful medical supervision the lowest effective dose.

Head Injury

need injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of carebrospinal fluid pressure, and may be markedly exaggerated in the presence of head flurry, intracranal lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupilary response and consciousness which may obscure neurologic signs of further increases in efficiency may pressure in patients with head injuries.

Hypotensive Effect DxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood

pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as preventions or offer agreet which compromise escendor tree. Oxycodore may produce of the solid hypotension in articulatory parties. Devy offers, lest a project analyses of the morphin-hypotension and returned or the morphin-hypotension and produced and produced and produced by the drug may further reduce car their carbon to petients in circulatory shock, since vascellation produced by the drug may further reduce car their carbon and Produced receives.

PRECAUTIONS

Copied analysiscs have a narrow therapeutic Index in certain pastent populations, especially when com-brend with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analys-sia untwelf) the known risks of respiratory operession, altered merital state, and opioural hypotheria. Use of Doy Contin¹⁸ is associated with increased potential risks and should be used only with custion in the following conditions acute abondours adminiscrately cape (a, dodicions) of selessis (CNS depre-sions) or original control of the control of

The administration of oxygodone may obscure the diagnosis or clinical course in patients with acute abdom-inal conditions. Dvycodone may apparate convulsions in patients with convulsive disorders, and all opi-oids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

Non-combination with cuto userpressions. Open control to the contr

taken in combination with the usual doses of Do/Cortin.

Interactions with Mixed Apoints/Antaponist Opioid Analgesics
Aposts/stratoponist analgesics (i.e., pertazzone, aubuphne, and butorphanol) should be administered causion to a potient who has received or its receiving a course of therapy with a pure opioid aporest opics such as oxycodone. In this situation, mixed aponist-trapponist analgesics may reduce the analgetic of oxycodone andor may precipitate withinterval symptoms in these pullents.

Rehibitations Communications**

The Amelitations

**The Amelit

Ambunatory Surgery and Postoperative Use
OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management
of postoperative pain).
OxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not
been established.

been established.

OxyConflin is not indicated for pain in the postoperative period if the pain is mild or not expected to per-sist for an extended period of time.

OxyConflin* is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extend-ed period of time. Physicians should individualize treatment, moving from parenteral to oral analgesis: as appropriate (See American Pain Society guidelines).

Patients who are already receiving DxxContin* Tables as part of ongoing analgesic therapy may be safely confirmed on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (set DBSAEC AND ADMINISTRATION).

On/Contin and other morphine-like oploids have been shown to decrease bowell motify, lisus is a com-mon postoperative complication, especially after intra-abdominal surgery with opioid analogists. Caution should be taken to monitor for discreased bowell motify in postoperative patients receiving opioids. Standard support the therapy should be implemented.

Use in Pancreatic/Billiary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients billary tract disease, including acute pancreatris. Opioids like oxycodone may cause increases in the se

rance and Physical Dependence

Tolerance is the need for increasing doces of opioids to maintain a defined effect such as analysis in the absence of disease progression or other external factors). Physical dependence is maintenant by with drawal symptoms after abruict discontinuation of a drug upon administration of an arrangement, physical dependence and not unusual during chronic opioid therapy.

reactive are not account on the processor of the processor of the processor of the following: re-tries placed as the processor of the process

In general, opioids should not be abruptly discontinued.

Information for Patients/Caregivers

- information for Patients/Caregivers

 If clinically advisable, patients receiving DxyContin Tablets or their caregivers should be given the followinjointomation by the physicians, runses, charmacels, or caregiver.

 1. Patients should be aware that OxyContin Tablets on this noycodone, which is a morphine-like substance.

 2. Patients should be advised that OxyContin Tablets was entry on properly only if swallowed whole.

 DxyContin Tablets wit release all their contents at once if broken, chewied, or crushed, resulting in a risk or fall of verofice.
- Or man verticolor.

 P. Patients should be advised to report episodes of breakfrough pain and adverse experiences occurring during therapy, individualization of dosage is essential to make optimal use of this medication.

 Patients should be advised not to adjust the dose of DoyContin* without consulting the prescribing professional.

- fessional.

 5. Patients should be advised that OxyCordin may impair mental and or physical ability required for the per-formance of potentially hazardous tasks (e.g., driving, operating heavy machinery).

 6. Patients should not combine OxyCordin with alcohol or other central nervous system decreasers (sieep asis, tranquitizes) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or dealth.

 7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consist their physician regrading the effects of analysiscs and other drug use during regnancy on themselves and their unborn child.

- solves and their unborn child.

 8. Patients should be advised that OxyCordin is a potential drug of abuse. They should protect it from their, and it should never be given to anyone other than the individual for whom it was prescribed.

 9. Patients should be advised that they may pass empty matrix 'ghosts' (tablets) via coloisotmy or in the stool, and that this is of no concern since the active medication has already been absorbed. Pretires is should be advised that if they have been receiving treatment with OxyCordin for more than a twe weeks and cessation of therapy is indicated, if may be appropriate to bare the OxyCordin does, other than aburgly discontinue it, due to the risk of procepturely subfraved symptoms. They physician can provide a does schooled by accomplish a gradual discontinual and or the medication.

 1. Patiers should be instituation keyed by OxyCordin is a society size of of the reactation.

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with opport operations, either active or in remission, is for the management of pain recoding opioid analysesia.

Drug-Drug Interactions

Drug-Origi Interactions
Opicial analysiss, including DayCortin*, may enhance the neuronuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Daycodone is metabolized in part to oxymorphice via cyclortome P450 206. While this pathway may
be blocked by a variety of drugs (e.g., certain cardiovascular drugs) including amiodiarone and quintifies
as well as polycyclic artificipressiants), such blockade has not yet been shown to be of clinical significance
with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants
O(C)Onthit*, Nea do joid analysiscs, should be started at 1/2 to 1/2 of the usual dosage in patients who are concurredly receiving other central nervous system depressants including sectives or hyporotics, experient anesthetics, beneficially acting and-emplois, transgulaters, and actice Decisions experient anesthetics, beneficially acting and emplois, transgulaters, and actice Decisions experient anesthetics, beneficially experient solves of consolidation of coma may result. No specific interaction between occording and managine oxidates inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

patients taking this class of drugs is appropriate Carcinogenesis, Musagenesis, Impairment of Fertility Studies of exposeron to evaluate the carcinogenic potential have not been conducted. Oxycodore was not musagenic in the following assays: Arms Salmonela and E. coll test with and with-out metabolic activation at doses of up to 1000 µg/m1, and with advantage in the absence of metabolic activation at doses of up to 1000 µg/m1, and with advantage in the interest of the part of t

Pregnancy

regulatory

Transparie (Fields: — Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 6 maying and 55 maying, respectively. These doses are 3 and 46 times a burnan dose of 150 mg/day, based on mg/sp basis. The results dind reveal evidence of harm but here such as to exposition. There are, however, no adequate and well-controlled studies in pregnant women. Because arimal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

OxyContin' is not recommended for use in women during and immediately prior to labor and delivery because oral opicidis may cause respiratory depression in the newborn. Neonates whose mothers have been tak-ing oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth-Nursing Mothers Low concentrations of oxycodone have been detected in breast mik. Withdrawal symptoms can occur in breast-leeding infants when maternal administration of an opioid analysis is stopped. Ordinarily, rursing should not be undertaken white a patient is receiving OxyCordin because of the possibility of sedation and/or respiratory depression in the infant.

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.

Gertatric Use
In commodel pharmacokinetic studies in eidenty societics (greater than 65 years) the clearance of poycool appeared to be slightly reduced. Compared to young solds, the gissers concentrations of droycotione with created approximately 15%. Of the bris humber, 15% is 15% in clear to concentrations of droycotione with created approximately 15%. Of the bris humber, 15% and other) while 16% of 0,000,000 in clear 15% of the clear 15% of

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A study of CoyCordin in patients with hepetic imparement indicates greater plasma concentrations than those with normal function. The initiation of therapy at $1/_2$ the usual doses and careful dose thration is warranted.

In patients with renal impairment, as evidenced by decreased prestrinine clearance (<60 mL/min), the con-centrations of psycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Doseges should be adjusted according to the clinical sharpers.

Gender Differences

uniform underlined in pharmacolistic supplies a policy and pharmacolistic supplies a supplier and product for a product of the pharmacolistic supplies and product frequency of typical opioid adverse events than males, even after adjustment for body weight. The chiral revenance of a difference of this magnitude is low for a drug planted for the country of the pharmacolistic supplies and obseques, and there was no make female difference detected for efficacy or adverse

ADVERSE REACTIONS

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sommercio, azziness, viorintino, prumus, headacine, pri modulir, veseming, and astrineria, in many cases the frequency of three events during initiation of therapy may be minimized by careful individualization of starting dosage, sion titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cases or docrease in intensity as OxyConfin heraps is confirmed and some dispree of blet ance is developed.

Clinical trials comparing 0xyConfin with immediate-release oxyConfine and placebo revealed a similar adverse event profile between 0xyConfin and mimediate-release oxyConfine. The most common adverse events (>5%) reported by patients at least once during therapy were:

	OxyContin (n=227) (%)	Immediate- Release (n=225) (%)	Placebo (n=45) (%)	
Constigation	(23)	(26)	(7)	
Nausea	(23)	(27)	(11	
Somnolence	(23)	(24)	(4)	
Dizziness	(13)	(16)	(9)	
Pruritus	(13)	(12)	(2)	
Vomiting	(12)	(14)	(7)	
Headache	(7)	(8)	(7)	
Dry Mouth	(6)	(7)	(2)	
Asthenia	(6)	(7)	-	
Sweating	(5)	(6)	(2)	

The Indiewing achierase experiences were reported in DsyContin¹-treated patients with an incidence between 1% and 5%, in descending order of frequency they were ancrease, nenocursess, insormins, fever, confusion, dearthea, advantaging ingly, deposes, ands, anothey, expend, dyspones, postural hypotheristin, childs, twitch-ing, assistifis, ahnormal dreams, thought abnormalities, and incours.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were report-

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression
Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponalhemia, peripheral edema, syndrome of inappropri-ate antiduretic hormone secretion, thirst

are announced nonlinear societies, which Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hall from typerkinesia, typesthesia, typotonia, malaise, paresthesia, seizures, speech disorder, stupon tus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion Urogenital: amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, uri-

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progress-ing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death. Deaths due to overdose have been reported with abuse and misuse of CxyConfin*, by Ingesting, Inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is fur-ther increased when OxyConfin is abused concurrently with alcohol or other CNS depressants, including orther cnicks.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patient airway and institution of assisted or controlled ventilation. Supportive measures (including oxy-en and vasopressors) should be employed in the management of circulatory shock and purinovary edema accompanying overtose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or definance.

rillation. The pure opioid artagonists such as nalexone or natmetene are specific articlotes against respiratory deprison from opioid overdose. Opioid artagonists should not be administered in the absence of clinically is infinited in the properties of the control of the cont

Managing Expected Opioid Adverse Experiences

memerating expressive upward wateries experiences who are opioid-naive, will experience side effects. Most patients receiving opioids, sepsicially those who are opioid-naive, will experience side effects. Frequently the side effects from OxyCortin are transient, but may require evaluation and management. Adverse events such as constipation should be enricipated and related aggressively and prophylactically with a stim-ularit loadility and/or should softener. Patients do not usually become tolerant to the constipating effects of

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not per-sist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with antiemet-ics or other modalities may relieve these symptoms and should be considered.

Patients receiving OxyCordin* may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain line or no residual exycodone and are of no clinical consequence.

SAPETY AND HANDLING
OxyContin Takiets are said dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule if of the Controlled Substances Act.
OxyContin has been brayeled for their and diversion by criminals. Healthcare professionals should contact their State Prefessional Licersing Board or State Controlled Substances Automorphy in information on how to prevent and detect Josephson of their sound his product.
Store at 25°C (77°F), excursions permitted between 15°-30°C (59°-86°F).
Healthcare professionals can telephone Purchae Pharma's Medical Services Department (1-888-726-7535) for information on this product.

DEA Order Form Required

Purdue Pharma L.P., Stamford, CT 06901-3431 ©2001 Purdue Pharma L.P.

U.S. Patent Numbers 4,861,598; 4,970,075; 5,266,331; 5,508,042; 5,549,912; and 5,656,295





